IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Aberg *et al.*	**Confirmation No.:** 3537
Serial No.: 09/447,218	**Group Art Unit:** 1623
Filed: November 23, 1999	**Examiner:** L. Crane
For: METHODS FOR TREATING URTICARIA USING DESCARBOETHOXYLORATADINE	**Attorney Docket No.:** 4821-362-999 (JD 208423-999361)

DECLARATION OF DR. PAUL M. TARANTINO, JR.

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, PAUL M. TARANTINO, JR., Ph.D., declare and state as follows:

1. I am a citizen of United States and reside at 61 Summer Lane, Holden, MA 01520.

2. I received my Bachelor of Science degree in Biology from Villanova University, Villanova, PA in 1993. I received my Ph.D. degree in Pharmacology from University of Massachusetts Medical School, Worcester, MA in 1998.

3. After receiving my Ph.D., I was employed as a Staff Scientist, and then a Senior Scientist at GLSynthesis Inc. in Worcester, MA, from 1998 to 2001. In 2001, I was promoted to Director of Pharmacology at GLSynthesis Inc. and held that position until early 2002. In February 2002, I joined Sepracor Inc. ("Sepracor"), Marlborough, MA, as an Associate Director of Safety Pharmacology. Currently, I am Director of Safety Pharmacology at Sepracor. I have published in various peer-reviewed journals and presented my research at national and international meetings. A copy of my curriculum vitae is attached hereto as **Exhibit 1**.

4. Currently as the Director of Safety Pharmacology at Sepracor Inc., I am intimately involved in the process of drug development. My duties include the design and implementation of non-clinical safety programs including: study design, dosage selection, study initiation and monitoring. Non-clinical safety programs include, but are not limited to, *in vitro* assays and *in vivo* (*e.g.*, animal) studies. I regularly review reports concerning non-

clinical safety, and am involved in risk assessment and regulatory decisions concerning Sepracor's drug candidates. In particular, I extensively deal with toxicology and safety pharmacology related matters, including reviewing, maintaining and tracking records for all non-clinical toxicology and safety pharmacology studies and results at Sepracor.

5. I have reviewed the specification and claims of the present application. I have focused particular attention on Example 4 of the specification. In addition, I have read the Office Action dated August 8, 2005, attached hereto as **Exhibit 2**, and specifically, reviewed the Examiner's comments concerning Example 4. (*See* pages 8-9 of **Exhibit 2**).

6. I understand that the Examiner questions the significance of the data reported in Example 4 of the present application, in comparison with the data in Brandes *et al.*, *Journal of the National Cancer Institute*, 86(10): 770-775 (1994), in the context of what was known about certain potential adverse effects associated with loratadine and its metabolite descarboethoxyloratadine ("DCL") prior to December 30, 1994, the priority date of the present application. In particular, the Examiner states that it is unclear whether Example 4 of the present application shows "a real or imaginary difference in the capacity to promote neoplastic tissue growth in actual neoplasms" because "Brandes provides an examples [*sic*] of tests against real neoplastic-disease-infected cells while the data in the instant disclosure does not appear to provide a parallel disclosure." (**Exhibit 2**, page 9).

7. To assess the issues raised by the Examiner, I have reviewed the following additional materials:

1) Gleichmann *et al.*, "Immunotoxicology: supressive and stimulatory effects of drugs and environmental chemicals on the immune system," *Arch. Toxicol.*, 63(4): 257-273 (1989) ("Gleichmann"), attached hereto as **Exhibit 3**;
2) Vos, "Screening and Function Studies in Immunotoxicity Testing," *Vet. Q.*, 3: 190-195 (1981) ("Vos"), attached hereto as **Exhibit 4**;
3) Brandes *et al.*, "Enhanced Cancer Growth in Mice Administered Daily Human-Equivalent Doses of Some H_1-Antihistamines: Predictive In Vitro Correlates," *Journal of the National Cancer Institute*, 86(10): 770-775 (1994) ("Brandes"), attached hereto as **Exhibit 5**; and

4) Declaration of William W. Storms, M.D. ("Storms Declaration"), attached hereto as **Exhibit 6**.

8. I am, and have been prior to the preparation of this declaration, familiar with immunotoxicity assays such as those described in Vos and Gleichmann, which are discussed in more detail below.

I. Example 4 Shows that Descarboethoxyloratadine is Less Immunotoxic Than Loratadine

9. Immunotoxicity, in a pharmacological sense, is the degree to which a drug impairs a patient's immunological functions by, for example, suppressing the patient's immune system. (*See, e.g.*, Gleichmann, **Exhibit 3**, page 258, left column). Such toxicity or immunosuppressive effect of a drug candidate or a drug is seriously undesirable or unwanted because it impairs a patient's natural immune system and may render the patient susceptible to various infections and diseases, or expose the patient to an elevated risk of developing malignancy. (*Id.*, Abstract). Therefore, it is, and was prior to December 30, 1994, common to assess a compound's immunotoxicity when developing a drug.

10. One of the most well-accepted assays for assessing a compound's immunosuppressive effect is lymphocyte mitogenesis assay, similar to what is disclosed in Example 4 of the present specification. (*See, e.g.*, Vos, published in 1981, **Exhibit 4**, page 193). The assay disclosed in Example 4 in the present specification is designed to assess the degree of mitogenesis in cells that are treated with a specific mitogen for T cells (*e.g.*, concanavalin A) in the presence of a test compound, which, in the case of the instant application, is loratadine or DCL. The degree of inhibition of mitogenesis by the test compound correlates to immunotoxicity of that compound. In other words, the more inhibitory a compound is of mitogenesis, the more immunotoxic it is, and thus, that compound is less desirable as a drug candidate.

11. As shown in Example 4 of the present specification, IC_{50} values for inhibition of concanavalin A induced stimulation of lymphocytes were determined to be 1.0 μM and 5.6 μM for loratadine and DCL, respectively. Therefore, the results show that DCL is about 5-6 fold less potent in inhibiting mitogenesis, and thus less immunotoxic, than loratadine. Consequently, I would have concluded, based on the disclosure of Example 4 of

the present specification, that DCL would be more desirable as a drug candidate than loratadine with respect to immunotoxicity.

II. Example 4 Shows that Descarboethoxyloratadine is Less Likely to Promote Tumor than Loratadine

12. In addition to the immunotoxicities of DCL and loratadine, it would have been reasonable to conclude that Example 4 demonstrates that DCL is less likely to promote tumor growth than loratadine. This conclusion is based in part upon my review of Brandes, as explained below.

13. In Brandes, an *in vivo* assay for tumor promotion was performed, and the results were correlated with those obtained from five *in vitro* assays in an effort to devise a simple method that could provide useful information during preclinical development as to whether a compound would promote tumor growth. (Brandes, **Exhibit 5**, page 771, left column). In essence, Brandes was attempting to develop an *in vitro* surrogate model for evaluating the tumor promoting potential of a test article. One of the five *in vitro* assays performed in Brandes was lymphocyte mitogenesis test, which is virtually identical to what is disclosed in Example 4 of the present specification. (*Id.*, page 771, right column).

14. As a first step, the potencies of five antihistamines (*i.e.*, loratadine, astemizole, cetirizine, hydroxyzine, and doxylamine) in affecting tumor growth in rodents were examined in Brandes. (*Id.*, page 771, left column). The order of potencies in promoting tumor growth was determined to be: loratadine $\approx$ astemizole $\geq$ hydroxizine $\geq$ doxylamine $\approx$ cetirizine. (*Id.*, page 774, legend to Table 2).

15. Next, the potencies of the same five antihistamines in five different *in vitro* assays, one of which is the lymphocyte mitogenesis assay disclosed in Example 4, were examined. (*Id.*, page 771, left column). The results obtained from each of these five *in vitro* assays were correlated with those obtained from the *in vivo* assay described above. Upon correlating the results, the authors of Brandes concluded that "a significant correlation was observed between the rank order of potency of the antihistamines in all five in vitro assays and their rank order to enhance tumor growth in vivo." (*Id.*, page 772, right column) (emphasis added).

16. In particular, Brandes showed that the order of potencies of the five antihistamines, when determined by the lymphocyte mitogenesis test, was: loratadine $\geq$

astemizole ≥ hydroxyzine ≥ doxylamine ≥ cetirizine. (*Id.*, page 774, Table 2). Thus, the order of potencies of the five antihistamines determined using lymphocyte mitogenesis assay indeed correlated well to the order of potencies for tumor promotion determined using *in vivo* assay. Therefore, Brandes showed that an antihistaminic compound which is more immunotoxic, as determined by the lymphocyte mitogenesis test, is likely be more potent in promoting tumor.

17. Without being limited to a particular mechanism of action, given the results for antihistamines including loratadine in Brandes, it is my opinion that the immunotoxocity of loratadine or DCL was thought to correlate well to its tumor promotion potential prior to December 30, 1994. This is based in part on the fact that a compound with a higher immunotoxicity could interfere with the patient's immune defense against tumor, thereby promoting the growth of tumor. Conversely, a compound with a lower immunotoxicity could enable the patient's immune system to provide resistance against the growth of tumor.

18. As discussed above, Example 4 of the present specification indicates that DCL is 5 to 6 fold less immunotoxic than loratadine, when immunotoxicity is determined by the lymphocyte mitogenesis assay. Furthermore, it would have been reasonable to conclude that Example 4 demonstrates that DCL is less potent in promoting tumors than loratadine for the reasons discussed above. Consequently, I would have believed, based on the disclosure of Example 4 of the present specification, that DCL is a more desirable drug candidate than loratadine.

III. Brandes Suggests that Certain Non-sedating Antihistamines are More Immunotoxic and Potent in Promoting Tumor Growth than Others

19. The test results disclosed in Brandes, which was published prior to December 30, 1994, taught that loratadine and astemizole were most immunotoxic and most potent in promoting tumor among the five antihistamines tested. In addition, it was well-known that loratadine and astemizole were considered as members of a class of compounds known as "piperidine H_1 antagonists," as stated in Storms Declaration (*See* **Exhibit 6**, paragraph 13). Consequently, Brandes would have suggested to me that "piperidine H_1 antagonists," as a class, of which DCL is a member, are likely be more immunotoxic and potent in promoting tumor, as compared with other classes of antihistamines.

20. In sum, it is my opinion that: 1) the disclosure in Example 4 of the present application showed that DCL is less immunotoxic than loratadine, thereby demonstrating that DCL is more desirable as a drug candidate; and 2) the disclosure in Example 4, together with the teaching of Brandes, would have suggested that DCL is less potent in promoting tumor than loratadine, thereby demonstrating that DCL is more desirable as a drug candidate.

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that I make those statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: November 28, 2005

P. M. T. Jr.

PAUL M. TARANTINO, JR., Ph.D.